Chapter 13
Mature T/NK Proliferations/ Lymphomas and HL:
Diagnostic Approach

ABSTRACT

"T and NK-cell lymphoid proliferations and lymphomas" comprise nine groups with distinct cell origins, differentiation states, clinical features, localization, and cytomorphology. Most correspond to specific T or NK lineage. Still, few have a hybrid or indeterminate phenotype, including extranodal NK and T-cell lymphoma, EBV+ nodal T/NK-cell lymphoma, chronic active EBV disease, and severe mosquito bite allergy. The distinction between T- and NK cells is sometimes unclear. The main categories are Mature T-cell and NK-cell leukemias, Primary cutaneous T-cell lymphoid proliferations and lymphomas (CTCL), Intestinal T- and NK-cell lymphoid proliferations and lymphomas, Nodal T-Follicular Helper Cell Lymphomas, Peripheral T-cell lymphomas (PTCLs), EBV-related mature T-cell and NK-cell neoplasms, and Extranodal NK/T-cell lymphoma (ENKTL). HL comprises classical HL (cHL) and nodular lymphocyte predominant HL (NLPHL) subtypes.

INTRODUCTION

The main categories of mature T-cell and NK-cell lymphomas in the WHO 5th edition classification have been extended to include more entities with refined molecular pathogenesis and diagnostic criteria. *(*Alaggio et al., 2022*).*

Recently, the heterogeneity of Hodgkin lymphoma has been highlighted. While classic Hodgkin lymphoma (CHL) remains unchanged, nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) is now renamed nodular lymphocyte predominant B cell lymphoma (NLPBL) in recognition of the distinct pathologic, biologic, and clinical differences. (Tousseyn et al., 2023).

This chapter aims to explore the rationale of recent biological classification, molecular pathogenesis, and diagnostic approaches to the T/NK and HL. The implications on risk stratification and therapeutic decisions on these types of lymphoma with the role of novel targeted therapy. These objectives will be discussed through the following sections:

A. Mature T-cell and NK-cell lymphomas in the WHO 5th edition classification *(*Alaggio et al., 2022*),* including leukemic and non-leukemic entities

B. Hodgkin's lymphoma: Classic and Nodular lymphocyte predominance types

DOI: 10.4018/978-1-6684-5818-1.ch013

A. Mature T/NK Proliferations/Lymphomas

The main categories of mature T-cell and NK-cell lymphomas in the WHO5 classification *(*Alaggio et al., 2022*)* are grouped into Leukemic and Non-leukemic types.

MATURE T-CELL AND NK-CELL LEUKEMIAS

Mature T- and NK-cell neoplasms present primarily as leukemia and include the following entities:

1. ***T-prolymphocytic leukemia (T-PLL)*** is rare accounting for ~2% of all small lymphocytic leukemias in adults with a median age of 61. It typically presents with splenomegaly, lymphadenopathy, and leucocytosis frequently >100x109 /l. Less commonly, other organs and skin are involved. Up to 30% of patients are asymptomatic at diagnosis. *(*Sabattini, 2022*).* It arises from mature, antigen-experienced, non-conventional memory T-cells.

Most T-PLL have aberrant TCL1A or MTCP1 protooncogenes expression, leading to overexpression of TCL1 and non-productive TCR-A rearrangement and the transition of naïve T-cells into an expanding pool of memory T cells. The TCR-mediated activation is the genetic hallmark of TPLL. Protein kinase B Akt1 activation and nuclear transport promote cell proliferation. (*Shi & Jevremovic, 2022)*

The diagnostic criteria and workup of T-PLL include major and minor criteria as outlined in Table 1. The recommended workup is summarized in Table 14.2 *(*Staber et al., 2019*).*

Table 1. Requirements to establish the diagnosis of T-PLL (Staber et al., 2019)

Major Criteria	Minor Criteria (At Least One Required)
>5×10^9/L TPLL cells in peripheral blood or bone marrow	Abnormalities involving chromosome 11 (11q22.3; *ATM*)
T-cell clonality by PCR for TRB/TRG or by flow cytometry	Chromosome 8 abnormalities: idic(8)(p11), t(8;8), trisomy 8q
Abnormalities of 14q32 or Xq28 genes OR expression of *TCL1A/B*, or *MTCP1**	Abnormalities in chromosomes 5,12,13, 22, or complex karyotype
	Involvement of T-PLL specific site (e.g., splenomegaly, effusions)

Cases without TCL1A, TCL1B, or MTCP1 rearrangement or their respective overexpression constitute a TCL1-family negative T-PLL.

Table 2. Recommended workup for patients with T-PLL (Staber et al., 2019)

Assessments	General Practice	Clinical Trials
Initial Diagnosis		
History, physical examination	Always	Always
Blood count and differential count	Always	Always
Bone marrow aspirate and biopsy	When clinically indicated	Desirable
Biopsy or aspirate of the suspected involved site	When clinically indicated	Desirable
Immunophenotyping of blood lymphocytes	Always	Always
T-cell receptor rearrangement (TRB, TRG)	Always	Always
chromosome banding analysis	Desirable	Desirable

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